The University of Texas
Health Science Center at San Antonio
7703 Floyd Curl Drive
San Antonio, Texas 78284-7750

9811 '00 JUN -6 P1:58

Department of Pathology

(210) 567-4000

Direct Dial (210) 567-4088
Fax No. (210) 567-2367
e-mail jorgensen@uthscsa.edu

May 26, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. 00D-0109
Draft Guidance on Review Criteria for Assessment
of Antimicrobial Susceptibility Devices

Dear Sir or Madam:

I wish to comment on the draft guideline indicated above which establishes the criteria for clearance of antimicrobial susceptibility test devices. I have the perspective of both a laboratory director and user of FDA-cleared diagnostic products, and as someone that performs occasional studies for industry in order to obtain clearance for marketing of their devices.

First, I believe that the guidance draft is much clearer and more comprehensive than the original 1991 draft guidance document. I think that it is helpful to approach the analyses of study data using a more refined statistical basis. However, I think that the addition of confidence intervals with the performance criteria established at the lower of the 95% confidence interval has created a sharp increase in the required performance of new devices that is much more strict than the criteria applied to all of the currently cleared products. Specifically, I believe that the "Essential agreement" should remain at $\geq 90\%$ as the target value, and the confidence interval established around that target value. That would include the fact that the lower end of the confidence interval would be lower than 90% depending upon the sample size. Likewise, I think that the calculation of very major errors should use $\leq 1.5\%$ as the target value, and establish the confidence intervals around that value. In table 5, it is clear that the new criteria $\leq 1.5\%$ at the lower end of the confidence interval would effectively make the allowable number of errors more than twice as strict with small sample sizes. It is important to note that with many newer antibiotics, there very few resistant strains available for testing. Thus, on a

00D-0109

C2

species level, it would not be reasonable to expect that a large number of resistant isolates would be available for testing. Indeed, perhaps the allowable very major error rate should be increased to 2%, as suggested in the current draft version of the NCCLS M23-A2 guidance document.

The allowable rate of categorical errors should include the possibility of agreement of less than 90% when discrepancies occur within one doubling-dilution of the break point. This point has also been recognized and incorporated in the NCCLS M23-A2 draft document. It is not possible to exceed the acknowledged precision of such tests, i.e., the expected reproducibility of an MIC within a single dilution 95% of the time. At times one dilution differences next to a breakpoint can artificially inflate the categorical errors.

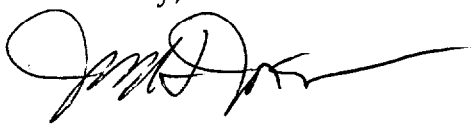
In determining the above calculations, I think that repeat testing of discrepant results should be allowed and should include both the reference and the test methods repeated in triplicate. The new values from both tests should be taken into consideration in resolving discrepancies. I think that the errors should be directly attibutable to the new device, not based upon the possibility of slight technical (human) errors. I noted the suggestion in the draft that the performance of the challenge strain collection must conform to the expected phenotypic results. However, if results are not as previously determined, then repeat testing should be performed in order to determine if there was a procedural problem in performance of the test or a genetic change in the challenge strain. That point can be answered in many cases by simply repeating both the test and reference methods. I further believe that all on-scale values, not just those ± 2 $\log_2$ dilutions of the breakpoints should be used in assessing the performance of a new device.

I agree that it is critical to precisely standardize the inoculum density of the reference and test methods used during the clinical trials. However, I think that this can best be accomplished using a photometric device rather than performing a large number of individual colony counts. A simple counter top photometric device calibrated using McFarland 0.5 or 1.0 turbidity standards should be used as specified in NCCLS M7-A5. The inoculum density in the reference and test device should be determined initially and periodically using *E. coli* ATCC 25922. The target inoculum density should be 5×10^5 CFU/ml (range $3 - 7 \times 10^5$ CFU/ml). It would be unrealistic to perform colony counts on all of the other NCCLS QC strains with insistence that they always provide results within the range $3 - 7 \times 10^5$ /ml.

Lastly, I am pleased to see that the ambiguous statements regarding use of alternative test methods for error prone drug-organism combinations has been removed from the draft. It has been a constant source of confusion for clinical laboratories.

I hope that these comments will be viewed as constructive criticism of a much improved guidance document. My main concerns are that the refined statistical approach to calculation of errors does not make the acceptability of test performance unreasonable and inequitable with the devices already licensed. My other major concern is that repeat testing for resolution of discrepancies should be allowed. Thank you for considering my comments.

Sincerely,



James H. Jorgensen, Ph.D.
Professor

"OFFICIAL BUSINESS
STATE OF TEXAS
STATE PENALTY
FOR PRIVATE USE"

Return Service Requested

PRESORTED FIRST CLASS

SAN ANTONIO MAY 30'00 TX

U.S. POSTAGE 00.525

H METER 546432

THE UNIVERSITY OF TEXAS
HEALTH SCIENCE CENTER at SAN ANTONIO
MAIL CODE _____
DEPT. _____
7703 FLOYD CURL DRIVE
SAN ANTONIO, TEXAS 78229-3900

DOCKETS MANAGEMENT BRANCH (HFA-305)
FOOD AND DRUG ADMINISTRATION
5630 FISHERS LANE
ROOM 1061
ROCKVILLE, MD 20852